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Effective Protein Interactions in a Coarse-Grained Model for Lipid Membranes

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A simple coarse-grained model for self-assembling lipid membranes is presented. The "lipids" are represented by short linear spring-bead chains, which self-assemble to membranes due to the presence of a computationally cheap "phantom" solvent environment. These membranes may contain "transmembrane proteins", represented by cylinders with diameters corresponding to the diameter of an α-helix. The system is studied by Monte Carlo simulations at constant pressure using a parallel code with a newly devised domain decomposition scheme. The effective interactions between two proteins are calculated for different lipid-protein interactions and compared with the predictions of an elastic theory.

1 Motivation

Biomembranes play a central role in both the structure and function of all biological cells[8]. They serve as an interface between different areas within a cell. A biomembrane, however, is not only a passive interface, but it plays an active role in the transport of molecules and information from one side of the cell to the other.

The biomembrane consists of a liquid-like bilayer of amphiphile lipids, into which membrane-proteins and other macromolecules are inserted. These proteins, e.g. receptors, enzymes and ion channels, are the biochemically active components. Their functions are very versatile: transport (exchange of material through the membrane), enzyme activity, signal transmission (receptors), cell connection, cell-cell recognition.

Both lipid-mediated interactions between proteins included in the membrane and the influence of such inclusions on lipid bilayers, have been intensively investigated for some time[9, 15, 16]. On the one hand the indirect interaction effects obtained by the lipids contribute significantly to the entire interaction between membrane proteins[3, 11]. On the other hand the direct electrostatic interaction effects in biologically relevant constellations become predominantly shielded by the aqueous environment of the membrane[2, 22].

Proteins affect the lateral structure of the lipid membrane: the number of possible conformations of the lipids in the proximity of proteins is reduced[3]. In multicomponent membranes, some lipid components are enriched[7]. Particularly dramatic effects can occur in two-phase areas – with the presence of sufficiently many proteins, the two phases may mix under certain circumstances, and one observes instead of a phase separation a heterogeneous structure of small domains[17, 18]. A protein-induced phase separation is also possible under certain circumstances[19]. Such phenomena have great practical importance, since the lateral structure of membranes is closely connected to its functionality. Apart from direct protein-protein interactions there are also different factors that can induce indirect interactions[9]. These are in particular:

1. Hydrophobic mismatch. This factor will come into play, if the length of the hydrophobic region of a transmembrane protein and the thickness of the membrane do not fit.
2. Disturbance of the local structure. The lipids in the environment of a protein lose their freedom of translation or conformation.
3. Membrane fluctuations. Proteins or other inclusions affect the fluctuation spectrum of membranes and limit it.

Different kinds of membrane proteins provide different characteristics of biomembranes. Protein interactions are of great importance to the functionality of the membrane. The indirect, lipid mediated interactions contribute significantly to the entire interaction between membrane proteins.

2 Coarse-Grained Bilayer Model

Our model consists of a self-assembled bilayer of lipids in a solvent environment[6]. The lipids are represented by chains of six tail beads of diameter σ_t and one slightly larger head-bead of diameter σ_h.

Beads not connected with each other interact via a truncated and shifted Lennard-Jones potential:

$$V_{\text{LJ, shifed}}(r) = \begin{cases} \epsilon \left(\left(\frac{\sigma}{r}\right)^{12} - 2\left(\frac{\sigma}{r}\right)^{6} + V_{\text{shift}} \right) & \text{, if } r < r_c \\ 0 & \text{, otherwise} \end{cases} \tag{1}$$

The parameter σ is the mean value of the diameters of the interacting beads. Head-head and head-tail interactions are purely repulsive ($r_c = \sigma$) and tail-tail interactions also have an attractive part ($r_c = 2\sigma$). The adjacent beads of the lipid chain are bound to each other by a finite extensible nonlinear elastic potential (FENE potential):

$$V_{\text{FENE}}(r) = -\frac{1}{2}\epsilon(\Delta r_{\text{max}})^2 \log\left(1 - \left(\frac{r - r_0}{\Delta r_{\text{max}}}\right)^2\right) \tag{2}$$

Additionally, chains are given a bending stiffness by a bond-angle potential:

$$V_{BA}(\theta) = \epsilon(1 - \cos(\theta)) \tag{3}$$

The solvent environment is represented by explicit solvent beads[13]. They behave like unbounded head beads, except for not interacting with each other. Figure 1 shows the phase diagram of our model[12].

3 Coarse-Grained Protein Model

The proteins are modelled as cylinders. The diameter of these cylinders correspond to that of an α-helix. The proteins are free to move in the xy-plane. The interaction in the xy-plane is represented by a Lennard-Jones kind of potential:

$$V_{\text{LJ, shifed}}(r) = \begin{cases} \epsilon \left(\left(\frac{\sigma}{r - r_{ir}}\right)^{12} - 2\left(\frac{\sigma}{r - r_{ir}}\right)^{6} + V_{\text{shift}} \right) & \text{, if } r - r_{ir} < r_c \\ 0 & \text{, otherwise} \end{cases} \tag{4}$$

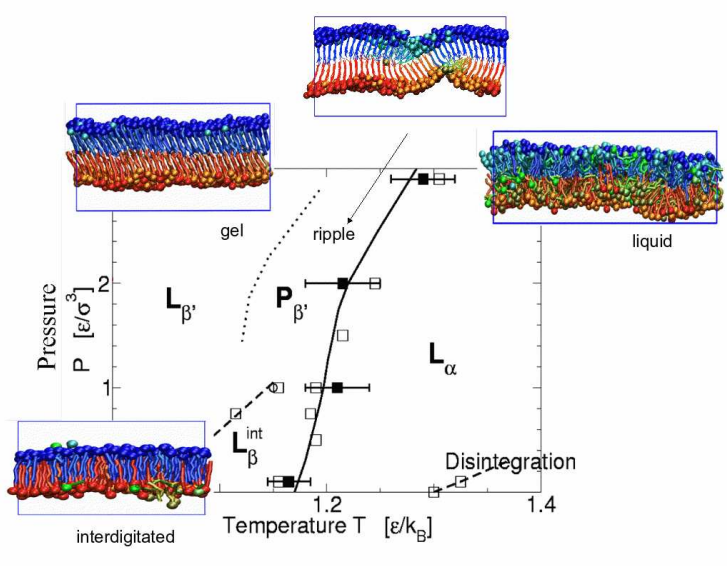

Figure 1. Phase diagram of our lipid model.

The interaction between the proteins and the head and solvent beads is purely repulsive. The interaction with the tail beads is also repulsive. For the tail-protein interaction there is an additional attractive component that depends on the z-distance between the tail bead and the protein.

4 Methods

The system is simulated using Monte Carlo methods at constant pressure and temperature with periodic boundary conditions. The simulation box is allowed to fluctuate during the simulation, i.e., we have additional volume and shape moves besides the moves of the beads.

The programme is parallelised using a geometrical decomposition[20,21]. The idea is to define "active regions", represented by the light blue areas in figure 2. Each processor gets one of these active regions. The distance between the regions is a little bit larger than the maximum interaction range of the beads. This is important to avoid interactions between beads in various active regions. Only the particles inside the active regions will be moved during a Monte Carlo step. Moves out of the active region will be rejected. To make sure that ergodicity is fulfilled, the offset of the active regions, represented by the red arrow in figure 2, is regularly moved randomly.

5 Lipid Bilayer with Two Proteins in the Fluid Phase

We simulate a lipid bilayer with two proteins in the fluid phase L_α for different protein-tail interaction strengths ϵ_{pt}, figure 3. The initial distance of the proteins is chosen such

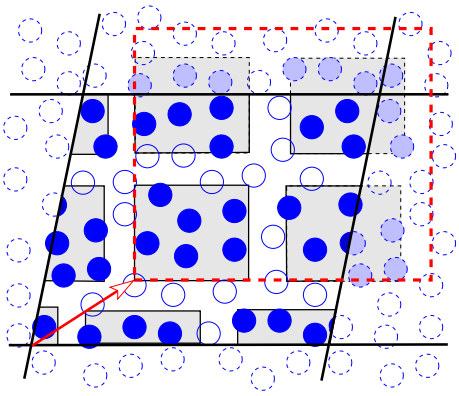

Figure 2. Parallelisation using a geometrical decomposition scheme.

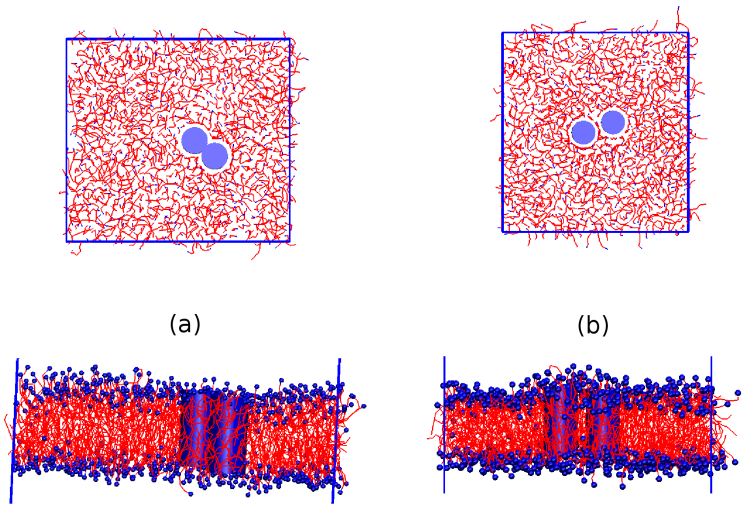

Figure 3. Lipid bilayer with two proteins in the fluid phase L_α: (a) weak interaction between proteins and tails (b) strong interaction between proteins and tails.

that they just touch each other. If the protein-tail interaction is weak, the proteins will stay next to each other and move together during the whole simulation. If the protein-tail interaction is stronger, the proteins will remain separated by a layer of one or two lipids. The membrane clearly is curved around the proteins.

From the pair distribution function $g(r)$ as a function of the protein-protein distance we can calculate the effective pair protein-protein interaction *via*:

$$w(r) = -k_B T \ln g(r) \tag{5}$$

$w(r)$ is the effective pair potential, k_B is the Boltzmann constant and T is the tempera-

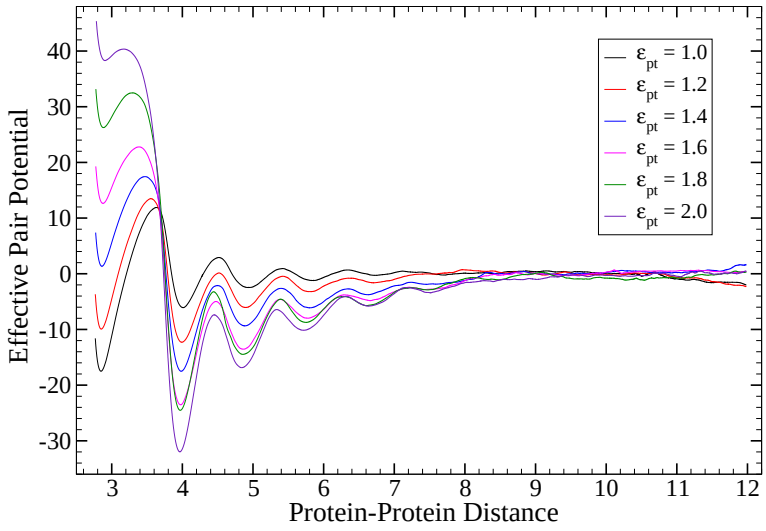

Figure 4. Effective pair potential between two proteins in the fluid phase.

ture. The pair distribution function is obtained by an umbrella sampling procedure as a function of the protein-protein distance. We first make several independent simulations i (preruns), where we contrain the protein-protein distance to stay within a given range $r \in [r_{min,i}, r_{max,i}]$. The windows $[r_{min,i}, r_{max,i}]$ overlap. From these prerun simulations, we deduce an estimate for the distribution of distances $h(r)$ in each window. Then we make a second run in each window, using $1/h(r)$ as a reweighting function to improve the statistics in the valleys. This gives us unnormalized pieces of $g(r)$ in each window. Finally, we put all these pieces together. The result is shown in Figure 4 for different values for the protein-tail interactions strength.

When analysing the effective pair potential different mechanisms seem to be important. On the one hand there is a layering effect. The proteins prefer distances where they are separated by a layer of one, two, ... lipids. On the other hand, there is a smoother interaction contribution, which presumably comes from a hydrophobic mismatch – the configuration snapshots (Figure 3) show that the membrane thickness is enhanced in the vicinity of the proteins. This lowers the curves if the protein-tail interaction is high. The first minimum corresponds to the region where the proteins are in direct contact. Note that the direct interaction between proteins is purely repulsive; however, an attractive depletion interaction is mediated by the solvent and the lipids. The final behaviour of the proteins is determined by the interplay of the different factors. If the tail-protein interaction is low, the effective contact interaction dominates. If the tail-protein interaction is high, the hydrophobic mismatch energy seems to dominate.

To assess the latter more quantitatively, we relate our results with the predictions of the elastic theory of membrane-induced interactions between inclusions by Aranda-Espinoza et al[1]. This theory describes a membrane as a system of two coupled elastic sheets (monolayers), taking into account their area compressibility, bending rigidity, and the individual spontaneous curvature. To extract the elastic parameters in our system, we have determined

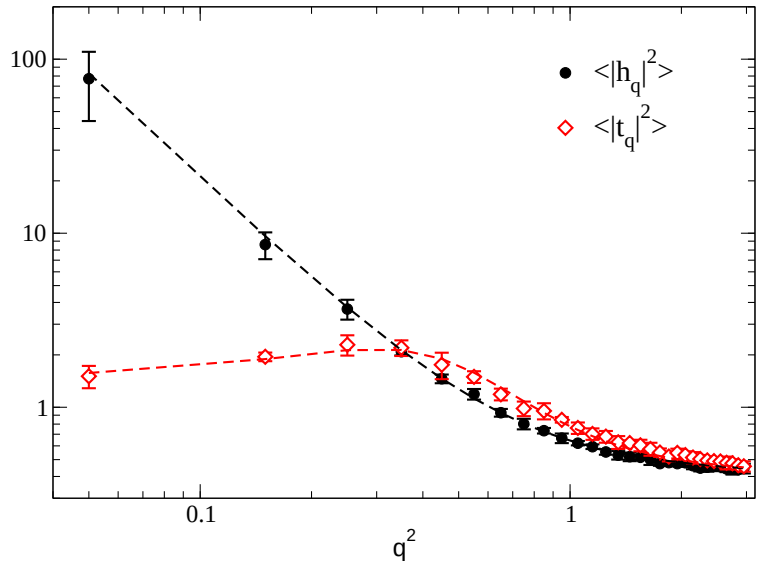

Figure 5. Capillary wave spectrum $< |h_q|^2 >$ (black circles) and thickness fluctuation spectrum $< |t_q|^2 >$ (red diamonds) of pure lipid membrane with fit to the elastic theory[4] (dashed lines). Both curves have been fitted simultaneously.

the fluctuation spectra of membrane position (capillary waves) and membrane thickness in pure membranes and fitted them to the elastic theory of Brannigan and Brown[4]. Figure 5 shows that the fit works very nicely. It provides values for the bending rigidity and the compressibility modulus. The latter is consistent with independent measurements of the lipid area as a function of membrane tension[10]. The remaining elastic parameter, the spontaneous curvature, has been calculated from the first moment of the pressure profile[14].

The elastic theory not only makes predictions for the interaction between two proteins, but also for the distortion of the membrane close to a single protein. Therefore, we have also studied a system with only one protein, and evaluated the thickness profile $u(r)$, *i.e.*, the distance between head beads in the upper and lower layer, as a function of the distance to the protein r. Figure 6 (left) shows that the hydrophobic mismatch seems to play an important role. At strong protein-tail interaction the membrane gets distorted.

The theory captures the distortion, but quantitatively, it does not agree with the simulation data. It predicts strong oscillations, which are not seen in the simulations. We have also evaluated the effective interaction potential (Figure 6, right). Even taking into account that the theory is not designed to capture layering effects, the agreement is still not good.

Hence the simple, straightforward application of the elastic theory fails to explain the findings of our simulation. More refined versions of the theory[5] might provide a remedy. It is also possible that additional factors have to be taken into account. For example, the vicinity of the protein will most likely affect the spontaneous curvature locally.

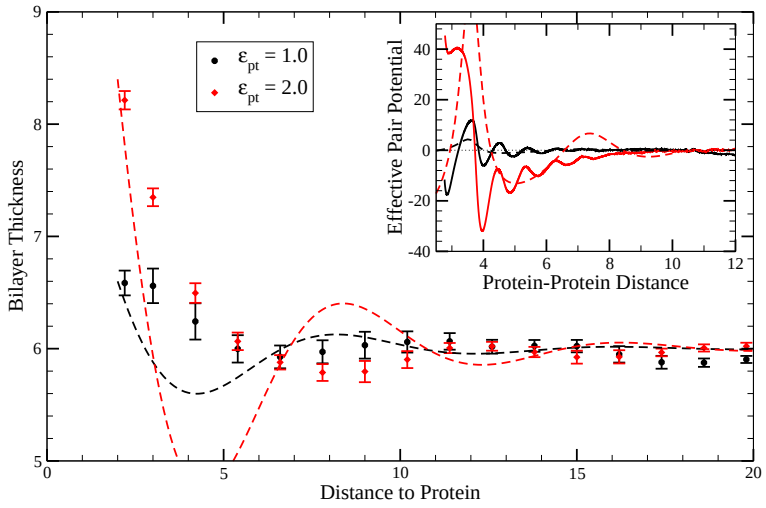

Figure 6. Comparison of the simulation data with the predictions of the elastic theory. Main panel: Thickness of a lipid bilayer depending on the distance to the protein for different protein-lipid interactions as indicated. Points are simulation data, dashed lines correspond to the theory with one fitting parameter, the relative distortion Δ_0 at contact. Inset: Effective protein-protein interactions for the same parameter values. Data are the same as in Figure 4 (solid lines). Dashed lines indicate theoretical prediction for the same values of Δ_0 as in the main panel.

Acknowledgments

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